



WORLD HEALTH ORGANIZATION  
ORGANISATION MONDIALE DE LA SANTÉ

MEETING ON INTERNATIONAL DRUG MONITORING -  
The Role of National Co-ordinating Centres

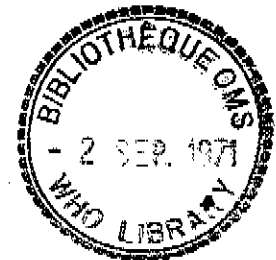
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THE UNITED KINGDOM DRUG MONITORING SYSTEM

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1. Introduction

In the United Kingdom the responsibility for monitoring the adverse effects of drugs is undertaken by a Sub-Committee of the Committee on Safety of Drugs.\* The Adverse Reactions Sub-Committee consists of twelve members who have special experience in many different clinical areas. It has a full-time professional staff of three doctors and also employs, on a part-time basis, a team of between 40 and 50 medically qualified field-workers.

The Committee started its work in 1963 and began to receive appreciable numbers of notifications of suspected adverse reactions in 1964. So far some 25,000 reports have been assembled. About half have been made by general practitioners, one-third by hospital residents or consultants and the remainder by family-planning clinic doctors, coroners, or dental surgeons. Useful information is also obtained from death certificates of patients who have died as a result of adverse reactions to drugs, and a small number of events are reported by the pharmaceutical industry.

While clinical trials should reveal the nature and incidence of common side-effects, the limited numbers of patients who can be studied preclude the detection, except by extreme chance, of the more serious and rare effects, which may perhaps affect only one patient among every 10,000 treated.

In the past, the Committee has requested the professions to report all reactions, however trivial, to newly introduced drugs and all serious and unusual reaction to other drugs. In practice, the majority of the reports have described comparatively serious and uncommon events (at least 10% are fatal) and much of the Committee's time has been spent on the assessment of reactions such as jaundice, blood dyscrasias or thromboembolism. Experience has suggested that reports of trivial events are of little value and the Committee has decided not to burden doctors with the work of reporting them.

\* Renamed the Committee on Safety of Medicines under the Medicines Act of 1968.

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## 2. Registration and coding of reports

All reports to the Committee are processed in strict confidence. The sources of the reports and the methods by which they are made are shown in Tables I and II respectively. It can be seen that the reply-paid postcard (figure 1) usually referred to as the "yellow card", has proved to be a most effective means for reporting, accounting for nearly 80% of the input. The format of the yellow card is very similar to that of the document used by national centres for reporting adverse reactions to the WHO Drug Monitoring Project. The coding procedure is also very similar. At present, all combinations of drug and reaction, however unlikely they are to be causally related, are processed using a therapeutically-based five-digit drug code. The simple adverse reaction code currently in use will probably be replaced by the more detailed WHO code once a more sophisticated data-processing system has been developed.

Yellow cards and other documents are filed chronologically in approximately 600 drug-files. Where more than one drug was given, tracer cards are placed in the appropriate files so that all the documents relating to one drug can be retrieved manually with considerable speed. The documents are stored in transparent plastic wallets, an important practical refinement of the case-files, which has facilitated rapid assessment of their contents, because they can be read without removing them from the wallets and rarely get lost or misfiled.

## 3. Recognition of new hazards

The computer programme currently in use enables the Committee to obtain simple tabulations of the reactions that have been reported under the approved names of the individual drugs. The computer can also be used for file-retrieval, but it is not yet possible to analyse the data in such a way that "signals" are generated which would draw the attention of the monitoring staff to potential hazards that might not have been identified during routine inspection of the reports. The data can be analysed in various ways in order to estimate the reported incidence or to obtain comparisons of the pattern of reactions to related drugs.

In the United Kingdom it is possible to obtain accurate estimates for the number of prescriptions and the total quantities of drugs that have been prescribed by general practitioners. These estimates account for perhaps 85% of all drug-use in the country. Using these estimates it is possible to calculate the "reported incidence" of adverse reactions.

On several occasions new hazards have come to light as a result of comparisons of the pattern of reactions that have been reported to related drugs. The "reaction profile" of a drug is usually prepared by calculating the proportion of reports of each type of reaction among the total number of reports that have been received for a particular drug.

An example of this method of analysis is provided by the profiles of five analgesic drugs shown in figure 2. It can be seen that while the pattern of suspected reactions to phenylbutazone and oxyphenbutazone are virtually identical,

there are quite marked differences in the profiles of the other drugs. That for ibufenac, showed a large predominance of reports of jaundice. Indomethacin shows a high proportion of central nervous disturbances while mefenamic acid shows a high proportion of gastro-intestinal symptoms.

Using prescription data, it is sometimes possible to demonstrate differences in the reported incidence of reactions to related products. In 1966, for example, an apparent difference was noted in the pattern of reactions to oral contraceptives containing mestranol or ethinylloestradiol. While the sales of products containing one or other oestrogen were almost equal, there were appreciably more reports of thromboembolic disease following the use of mestranol-containing oral contraceptive preparations that would have been expected on the basis of the estimates of sales. Some three years later it was possible to demonstrate that the increase risk of thromboembolism was more likely to be related to the oestrogen content of oral contraceptive preparations, rather than to chemical differences between the two oestrogens. Subsequently, similar data were supplied by the Swedish and Danish Adverse Reactions Committees and, when analysed in the same way, valuable corroborative evidence of the UK results was obtained (Inman et al. 1970).

The "reported incidence" of adverse reactions is much less than the actual incidence, because only a small proportion of the events that actually occur are reported to the Committee. In spite of publicity surrounding the problem of oral contraceptives and thrombosis, Inman and Vessey (1968) found, during the course of a retrospective enquiry into the deaths of women of child-bearing age, that only two of 53 general practitioners, who knew that their patient was using oral contraceptives at the time she died of thrombosis, had reported the death to the Committee. In another situation which attracted much less publicity, Inman and Adelstein (1969) suggested that perhaps 3,500 asthmatics might have died as a result of over-use of pressurised aerosols containing bronchodilating drugs. Only a handful of reports of sudden deaths had been sent to the Committee during the period of nearly seven years before the hazard became generally recognized.

Possibly because of the long interval between exposure to a drug during early pregnancy and the subsequent birth of a deformed baby, so few doctors have suspected and reported possible associations of this kind that the voluntary system cannot be regarded, at present, as an effective means of providing "early warning" of possible human teratogens.

#### 4. Investigation of a new hazard

A large number of "early warnings" are derived from the voluntary reporting system, and it is sometimes quite difficult to decide on the priority that should be given for further investigation of possible hazards. It is usually necessary to follow-up individual reports in order to ascertain the outcome of the reaction and any other factors, including concurrently administered drugs, which might provide an alternative explanation for the event.

The Committee currently employs between 40 and 50 medically qualified field-workers for this purpose and intends to increase this number to about 100 in the future. When their preliminary investigation suggests that the reaction may be

causally related to the use of a drug, the Committee may decide to bring this immediately to the attention of the professions or they may delay publication of a warning until further studies have confirmed causal relationship and possibly established the incidence of the reactions.

Occasionally it may be possible to study a problem in small numbers of patients under laboratory conditions. If the reaction occurs infrequently, the Committee may refer to a group of doctors conducting intensive hospital monitoring of large numbers of patients. When, on the other hand, the reaction is very rare, large populations may need to be studied either prospectively or retrospectively.

#### 5. Provision of information to the medical professions

The Committee's professional staff undertake extensive correspondence with individual physicians who have reported adverse reactions or who enquire about them.

The Committee has issued nine pamphlets in its Adverse Reaction Series and its officers have published letters and papers in medical journals on several occasions.

The unpredictable response of the national news media to statements by the Committee or to the publication of scientific papers has led to difficulties. It is not easy to inform the medical professions about the existence of hazards associated with the use of drugs without running the risk that some of the patients who are taking them may read about this warning and become alarmed. The Committee endeavours to keep pharmaceutical companies informed of any dangers that come to their attention, and frequently check sales-literature in order to ensure that information concerning side effects and adverse reactions is correct.

The United Kingdom has made a major contribution to the input of reports of suspected adverse reactions handled by the WHO Drug Monitoring System in Geneva. In the development of improved facilities for automatic data processing in the United Kingdom, consideration is being given for the need for two-way exchange of information between the national and international centres and to the possibility of effecting this exchange on magnetic tape rather than by the more cumbersome method of copying original documents.

#### 6. Summary

A monitoring system based on the voluntary reporting of suspected adverse reactions to drugs has been operating in the United Kingdom for seven years. Much valuable experience has been gained and the monitor has provided a number of warnings of new drug safety problems. Much of the success of the operation stems from two capabilities not enjoyed by all countries undertaking similar work - the ability to obtain a denominator in the form of estimates of drug-usage and the ability to conduct field studies with the help of a team of medically qualified officers.

Once new problems have been identified, every effort is made to persuade specialists to undertake further research into them. Occasionally the Committee's own team of field workers may be engaged in epidemiological studies on a fairly large scale.

"Feed-back" of information concerning adverse reactions is largely conducted on an individual basis, but the Committee has also published a small number of pamphlets in its Adverse Reaction Series and its professional staff have produced occasional detailed scientific reports on various aspects of their work. New methods of communication are under active examination by the Committee.

R E F E R E N C E S

- Inman, W.H.W., Vessey, M.P., Westerholm, B. and Englund, A. (1970), Brit. med. J. 2, 203
- Inman, W.H.W., and Vessey, M.P. (1968) Brit. med. J. 2, 193
- Inman, W.H.W., and Adelstein, A.M. (1969), Lancet, 2, 279

TABLE I

Source of reports of suspected reactions  
(based on approximately 24,000 reports to the Committee 1964-1970)

<u>Source</u>	<u>% Total Input of Suspected Adverse Reactions</u>
General practitioner	54.0
Hospital resident	17.1
Consultant	17.0
Family planning clinic	7.4
Medical officer of health	1.5
Dental surgeon	0.9
Coroner	0.2
Others	1.9

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TABLE II  
Routes by which reports reached  
the Committee on Safety of Drugs (1964-1970)

<u>Route Reach</u>	<u>% Total Input of Reports</u>
"Yellow-card"	78.7
Letter from doctor	9.6
Drug company	5.4
Office of Population Statistics	4.2
Royal College of G.P.'s	0.9
Field workers	0.8
Case report in major UK journal	0.3
Others	0.1

IN CONFIDENCE: NOTIFICATION OF TOXICITY OR SIDE EFFECTS **Fig. 1.**

Name of Patient: (see note 8)			Name and Address of Person Reporting Reaction:			
Sex		Date of Birth				
OTHER DRUGS	DRUG	ROUTE	DOSE	Began	Terminated	DISORDER OR REASON FOR USE
	S					
REACTION (List in order of severity)				Date of Onset	Duration	OUTCOME (eg fatal: recovered)

Additional Notes

Please complete if known:
Height
Weight
Blood Group
Batch No (Vaccines)
Signed

Date

**NOTES FOR GUIDANCE IN REPORTING ADVERSE REACTIONS**

- 1 Please do not be deterred from reporting because some details about the patient or the reaction are not available. An adverse reaction is any reaction which is noxious or unintended and which occurs at doses normally used in man.
- 2 Please report all reactions of a serious, uncommon or unusual nature, but not familiar minor reactions with established drugs, such as dry mouth with belladonna. With new drugs however all reactions, no matter how trivial, should be reported.
- 3 Please give the Brand name of the drug if known.
- 4 Record the drug you suspect to have caused the reaction on the top line of the drug section (S). Record other drugs given concurrently or up to six months before the reaction. Do not include drugs used to treat the reaction unless these have produced a further reaction.
- 5 Where more than one reaction has been observed, record the one that was considered to be the most dangerous or distressing to the patient on the top line of the reaction section.
- 6 Record a separate 'outcome' for each reaction listed.
- 7 Please be as specific as possible about dates.
- 8 The name is required, in strict confidence, only to allow linkage of two or more reports on the same person.

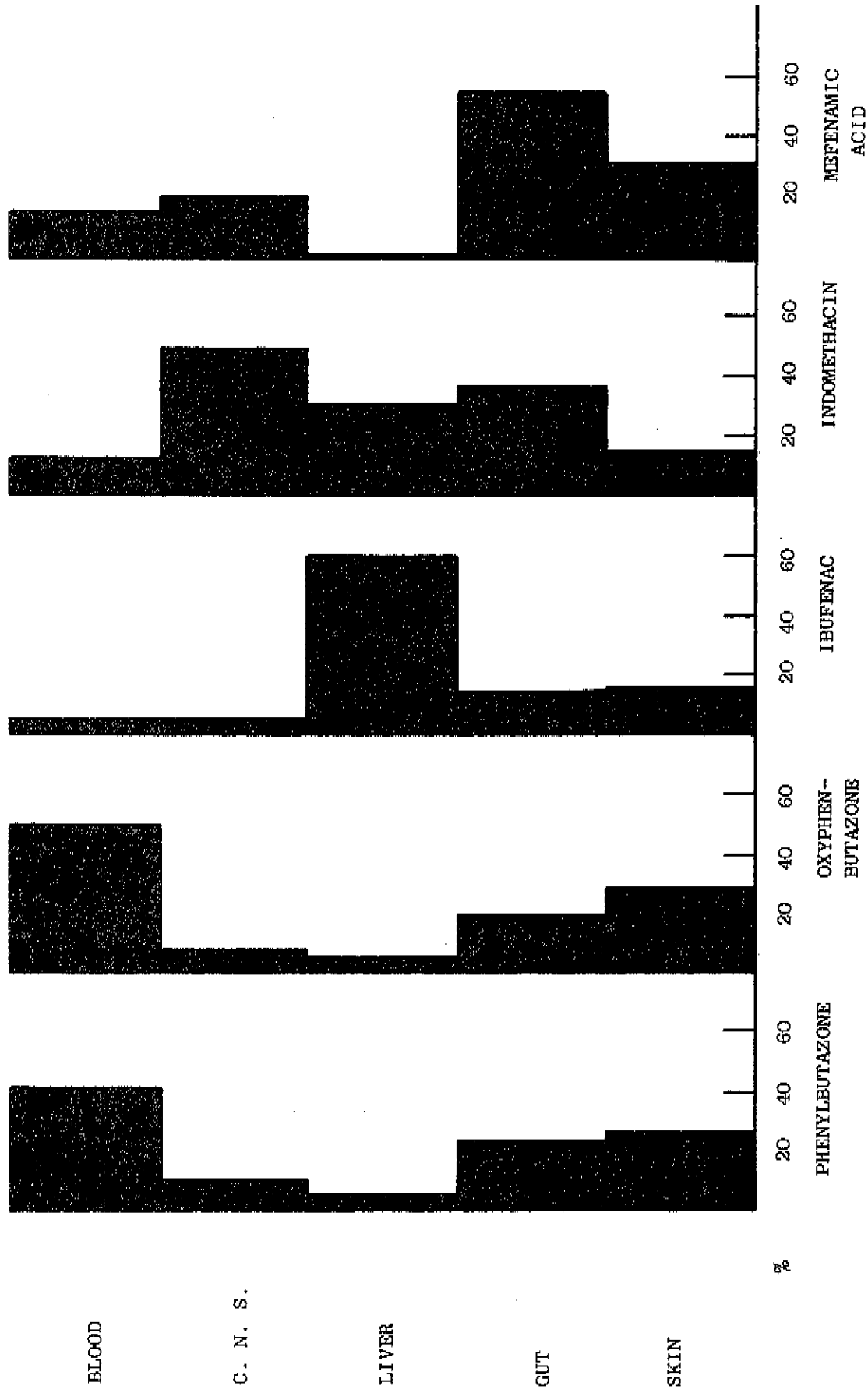


FIG. 2. REACTION PROFILES OF FIVE ANALGESIC DRUGS